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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/778,672	02/07/2001	Hsu Ching-Hsaing	12774-002001	4367

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EXAMINER	
LI, QIAN JANICE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 09/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/778,672	CHING-HSAING ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 June 2004* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-33,35-39 and 41-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-33,35-39 and 41-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 February 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment and response filed 6/22/04 have been entered. Claims 26 and 35 have been amended, and claims 24-33, 35-39, 41-49 are pending and under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated. The arguments in 6/22/04 response would be addressed to the extent that they apply to current rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 24-33, 35-39, and 41-49 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Hsu et al* (US 5,958,891) and *Janeway Jr.* (Immunobiology, 1999), in

view of *Pouwels et al* (Intl J Food Microbial 1998;41:155-67) and *Medaglini et al* (PNAS 1995;92:6868-72, IDS/AI), for reasons of record and following.

1. In 6/22/04 response, under the subtitle "there is no motivation to combine references", applicants presented arguments with regard to the teaching of the Janeway reference concerning the nature of the antigen and routes of administration for inducing IgE response vs. instantly claimed invention for suppressing IgE response.

As an initial matter, in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, it is the combined teachings of the cited references that render the claimed invention obvious. Particularly, the *Janeway* reference supplemented the teaching of *Hsu et al, Pouwels et al,* and *Medaglini et al* by establishing that it is well known in the art that the IgE response could be suppressed by shifting the antibody response towards one dominated by IgG response, which provides a nexus and added motivation to combine the teaching of *Hsu et al* with that of *Pouwels et al,* and *Medaglini et al* because the recombinant bacteria as taught by *Pouwels et al,* and *Medaglini et al* would not only provide a proper carrier for oral administration of the nucleic acid expressing the dust mite allergen, but also help to shift the immune response to an IgG dominated one, and thus further suppress IgE response. In this way, *Janeway* provides motivation to combine the references, whereas the claimed

method steps and composition used are taught in *Hsu et al, Pouwels et al,* and *Medaglini et al* as previously discussed in detail. The many other benefits (motivations) for combining a nucleic acids expressing a dust mite allergen with a recombinant bacterial construct have been extensively discussed in the previous Office action (mailed 12/17/03, pages 5-7), thus will not be reiterated here. Applicant is reminded that the *Janeway* reference was cited to address applicant's argument that administration of the recombinant bacteria would induce an IgG response, and "enhancing an IgG production is conflicting with suppressing of IgE production". *Janeway* reference was cited to show that induction of an IgG response is a regulatory mechanism for suppressing IgE, thus treating allergy.

With respect to the teaching of *Janeway et al* concerning the nature of the antigen, apparently *Hsu et al* had taught that a dust mite antigen could be used for suppressing IgE response in the context of a nucleic acid vaccine, thus, this is not an issue here.

With respect to the route of presentation, *Janeway et al* observed clinically that "ALLERGENS ARE OFTEN DELIVERED TRANSMUCOSALLY AT LOW DOSE", THUS THE ROUTE MAY FAVOR IGE PRODUCTION" (emphasis added). This is a general teaching concerning inducing allergy with *any* allergen at a *low dose* in natural occurrence, it is not necessarily applicable in the instant tolerance strategy since the dust mite allergen has been expressed in sufficient amount to effectively inhibit an IgE response, and when combined with a recombinant commensal bacteria such as LAB, which had been taught to be highly efficient in protein expression, the dose would not be low. Further, induction

of *immune response* and *tolerance* is a complicated and not well-understood matter, the same approach could do both, for example, in addition to the cited teaching above, *Janeway et al* also teach, "THE RULES OF MUCOSAL IMMUNITY ARE POORLY UNDERSTOOD. ON THE ONE HAND, PRESENTATION OF SOLUBLE PROTEIN ANTIGENS BY THE ORAL ROUTE OFTEN RESULTS IN TOLERANCE, WHICH IS IMPORTANT GIVEN THE ENORMOUS LOAD OF FOODBORNE AND AIRBORNE ANTIGENS PRESENTED TO THE GUT AND RESPIRATORY TRACT. AS DISCUSSED IN SECTIONS 14-10 AND 13-28, THE ABILITY TO INDUCE TOLERANCE BY ORAL OR NASAL ADMINISTRATION OF ANTIGENS IS BEING EXPLORED AS A THERAPEUTIC MECHANISM FOR REDUCING UNWANTED IMMUNE RESPONSES" (§ 14-25). Apparently, oral delivery is known to be a route for tolerance too. *Malone et al* (US 6,110,898) teach delivering a recombinant immunogen and association with tolerance induction, "MUCOSAL ANTIGEN PRESENTATION CAN BE ASSOCIATED WITH EITHER IMMUNOLOGIC STIMULATION OR INDUCTION OF TOLERANCE", "LIKE THE SYSTEMIC IMMUNE COMPARTMENT, THE COMMON MUCOSAL IMMUNE SYSTEM REQUIRES MECHANISMS FOR SELECTIVE SWITCHING BETWEEN THE EXPANSION OF EFFECTOR CELLS AND THE INDUCTION OF TOLERANCE", "THE MECHANISM(S) INVOLVED IN SWITCHING BETWEEN INDUCTION OR SUPPRESSION OF MUCOSAL IMMUNE RESPONSES REMAIN TO BE RESOLVED"(Column 2). This teaching illustrated that the induction or suppression of an immune response depends on the results of many factors working in concert, thus even though the low dose mucosal route may favor an IgE response, it does not teaches away from the instant invention due to the complex nature of the immune response and because oral tolerance is a well known approach to induce tolerance.

2. In 6/22/04 response, under the subtitle "there is no reasonable expectation for the alleged combination", applicants relied on the arguments with regard to the teaching of the Janeway reference and asserted that the Office has not shown a reasonable expectation of success because a result in direct contradiction to Janeway cannot be reasonably expected.

With respect to the expectation of success for the combination, it is indicated in the previous Office actions that *Hsu et al* disclosed successful use of a nucleic acid expressing a dust mite allergen for inhibiting IgE response, *Pouwels et al,* and *Medaglini et al* disclose recombinant commensal bacteria constructs as vaccine carriers, and *Janeway* further established that the IgG response induced by administering the recombinant bacteria expressing an antigen would further aid the suppression of an IgE response. Hence, given the success taught by each reference, the ordinary skilled would have had a reasonable expectation of success when combining the references. The instant situation is amenable to the type of analysis set forth in In re Kerkhoven, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to produce a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Given the teaching of the prior art compositions of an expression vector encoding a dust mite allergen and a recombinant commensal bacteria expressing an allergen-all taught to be useful for the suppression of an IgE response, it would have been *prima facie* obvious to one of ordinary skill in the art to combine these

compositions to generate a new composition for the treatment of allergy with a reasonable expectation of success.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify and combine the methods taught by *Hsu et al*, *Janeway, Jr.*, *Pouwels et al,* and *Medaglini et al* by expressing the Der p5 allergen using the plasmid pSMB7 or alike such as those taught by *Pouwels et al* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention for the multiple beneficial effects of LAB as taught by *Pouwels et al*, as well as adopting the strategy as taught by *Janeway, Jr.* shifting the antibody response away from an IgE-dominated response toward one dominated by IgG. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary. Applicants are reminded that obviousness does not require absolute predictability of success; for obviousness under 35 U.S.C. § 103, all that is required is a reasonable expectation of success. See *In re O'Farrell*, 7 USPQ2d 1673 (CAFC 1988).

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Amy Nelson** can be reached on 571-272-0804. The fax numbers for the organization where this application or proceeding is assigned are **703-872-9306**.

Any inquiry of formal matters can be directed to the patent analyst, **Dianiece Jacobs**, whose telephone number is (571) 272-0532.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Q. Janice Li
Primary Examiner
Art Unit 1632

QL
September 10, 2004